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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/623,543	BRIDON ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,24,25,28,33-36,42,43,49,50 and 56-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *22,25,28,33,61 and 62* is/are allowed.

6)☒ Claim(s) *24,34-36,42,43,49,50,56-60 and 63-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 4/17/2008 in response to the previous Non-Final Office Action (10/18/2007) is acknowledged and has been entered.

Claims 22, 24-25, 28, 33-36, 42-43, 49-50 and 56-68 are currently pending and under consideration.

Information Disclosure Statement

The Information Disclosure Statement filed on 4/17/2008 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

New Rejections Necessitated by Applicants Amendments:

Claim Objections

Claims 57 and 63-66 are objected to because of the following informalities: Claim 57 recites "A composition comprising the conjugate of claim 50 in association with a pharmaceutically acceptable carrier". However, claim 50 is drawn to a method. Similarly, claims 63-66 recite "The method of claim 57....". However, claim 57 is drawn to a composition. As such, for examination purposes, claim 57 has been examined to the extent that it is the conjugate of claim 49 and claims 63-67 have been examiner to the extent that it is the method of claim 58.

Applicants are reminded that no new matter should be introduced by amendment to the specification, see MPEP 35 USC 132.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 recites the limitation "said blood component" in the first line of claim 24. However, independent claim 22, which claim 24 depends, does not appear to provide antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 34-36, 42-43, 49-50, 56-60 and 63-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davidson et al. (WO 97/41824, 13 November 1997/ IDS reference AM on sheet 1 of 3, February 2001) in view of Peeters et al. (J. Immunol Methods 1989; 120: 133-143, *of record*) and Sivam et al. (US 5,116,944, 1992).

Davidson et al. disclose (see page 43, Example 5, line 12) a kringle 5 peptide or ester thereof having an amino aid sequence which appears to be 100% identical to the currently claimed modified

peptide comprising SEQ ID NO: 8. Davidson et al. further teach a method of producing polyclonal antisera, wherein the kingle 5 peptide is linked to purified bovine serum albumin using glutaraldehyde (page 36, lines 5-9). Moreover, Davidson et al. teach (page 36, lines 12-15) that the kingle 5 peptide conjugated to a carrier protein such as BSA is than combined with an adjuvant mixture and injected subcutaneously into a suitable host such as a rabbit, sheep, or goat. Lastly, Davidson et al teach a method of treating a patient in need of anti-angiogenesis therapy comprising administering to said patients a compound containing a kringle 5 peptide (page 3, lines 14-22). With regards to the patients, the WO document teaches that patients which are treated include, but are not limited to, those with cancer, diabetic retinopathy, retinal neovascularization, and capillary neovascularization with atherosclerotic plaques (page 19, line 28 to page 20, line 16).

Davidson et al. does not explicitly teach the kringle 5 peptide is linked to albumin via a maleimido or succinimidyl group, wherein the maleimido or succinimidyl group reacts with a thiol group on albumin to form a covalent bond. Nor does Davidson et al teach a method of preparing a conjugate comprising reacting a kringle 5 peptide modified with a maleimido or succinimidyl group albumin, wherein said maleimido or succinimidyl group reacts with a thiol group of said albumin to form a covalent bond or a method of administering the conjugate for the treating a patient in need of anti-angiogenesis therapy.

Peeters et al. disclose a comparison of four bifunctional reagents for coupling peptides to proteins and the effect of the three moieties on the immunogenicity of the conjugates. The reference further teaches that cross linkers such as glutaraldehyde have been shown to elicit antibodies directed against the spacer (page 142, 2nd column, 1st paragraph). In contrast, Peeters et al. teach that the more flexible non-aromatic linker originating from MHS (succinimidyl 6-(N-maleimido)-n-hexanoate) is the bifunctional reagent of choice for coupling peptides to carrier proteins because is showed almost no linker specific antibody reactivity (Abstract). Peeters et al. further teach the synthesis (page 134, Figure 1) of protein-peptide conjugates, wherein an amino group on the carrier protein is linked to the bifunctional reagent which is further linked to the peptide via a thiol group.

Sivam et al. teach conjugates comprising a therapeutically effective proteinaceous active moiety linked to an albumin moiety. For example, the patent teaches that albumin may be derivatised by reaction of a free NH2 group with the activated ester moiety of a heterobifunctional

reagent such as SMCC and linked to a protein via reaction of a free sulfhydryl group on the protein with the maleimido or other appropriate reactive moiety of the heterobifunctional reagent (column 5, lines 20-28). Alternatively, the patent teaches that the protein may be derivatized with a heterobifunctional reagent and linked to albumin via reaction of a free sulfhydryl group on albumin with the maleimido or other appropriate reactive moiety of the heterobifunctional reagent (column 5, lines 28-36). Moreover, the patent teaches that the addition of albumin to proteinaceous active moieties increases their serum half-life properties, as well as, increase their solubility and reduce toxicity (column 3, lines 49-52).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use MHS instead of glutaraldehyde to link a carrier protein, such as bovine serum albumin, with a kringle 5 peptide in view of the teachings of Peeters et al.. One would have been motivated to do so because Peeters et al. teach that unlike glutaraldehyde, MHS has a low potential for immunogenicity directed against the linker. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using MHS instead of glutaraldehyde as taught by Peeters et al. to link a carrier protein, such as bovine serum albumin, with a kringle 5 peptide, one would achieve a peptide-linked to a carrier protein which generates antibodies which are not directed against the linker.

Similarly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the kingle 5 protein albumin conjugate as taught by Davidson et al. in view of Peeters et al. with MHS followed by reaction with a thiol group of albumin in view of the teachings of Sivam et al. One would have been motivated to do so because it is well known in the art as taught by Sivam et al. that conjugation of a peptide to albumin involves either derivitization of the peptide with a reactive group followed by reaction with a thiol group of albumin or derivitization of albumin with a reactive group followed by reaction of a thiol group of a peptide. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the kingle 5 protein taught by Davidson et al. with MHS followed by reaction a thiol group of albumin in view of the teachings of Sivam et al., one would achieve a method of producing a kingle 5-albumin conjugate.

Lastly, it would have *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a kringle 5 peptide-albumin conjugate as taught by Davidson et al.

to a patient in need of anti-angiogenic therapy in view of the teachings of Sivan et al. One would have been motivated to do so because Sivan et al. teach that the addition of albumin to proteinaceous active moieties increases their serum half-life properties, as well as, increase their solubility and reduce toxicity. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering a kringle 5 peptide-albumin conjugate as taught by Davidson et al. to a patient in need of anti-angiogenic therapy in view of the teachings of Sivan et al., one would achieve a method of increasing the serum half-life of the kringle 5-albumin conjugate.

(Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous rejection as they relate to the instant rejection. In response to the previous rejection, Applicants assert that the combination of Davidson et al. and Peeters et al. does not give reason to one of ordinary skill to form a conjugate through covalent binding with a native thiol group of a blood component. Thus, Applicants assert that the proposed combination would not yield a conjugate having the exact chemical structure as the conjugate recited in the claims. For example, Applicants assert that as conceded by the Examiner, Davidson et al. only teaches conjugates using glutaraldehyde as a crosslinking agent, and thus do not contemplate using the thiol groups of the carrier protein. However, Applicants assert that Peeters et al. does not remedy this deficiency since Peters et al. does not teach or suggest reacting native thiol groups (e.g., thiol groups of a blood component) in order to form the peptide-carrier protein conjugate. In particular, Applicants contend that Peeters et al. discloses three possibilities for modifying a carrier protein in order to make a suitable coupling partner to make conjugate, wherein none of the methods utilize the thiol group of the carrier protein in reaction with the maleimido group. As such, the combination of Davidson et al. with Peeters et al., does not give reason to prepare the presently claimed conjugates.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges and does not dispute Applicants assertions that Peeters et al. teaches three possibilities for modifying a carrier protein in order to make a suitable coupling partner to make a conjugate, wherein none of the methods utilize the thiol group of the carrier protein in reaction with the maleimido group. However, the Examiner recognizes that consistent with the Supreme Courts findings in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the following factors set forth in *Graham v. John Deere Co.,* 383 U.S.

1,148 U.S.P.Q. 459(1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. In the instant case, the scope/content of the prior art and the differences between the prior art and the claimed invention are as set forth above and incorporated herein. With regards to the level of ordinary skill in the art, those of skill in the art at the time the invention was made recognize that the methodology of conjugating peptides to albumin has been practiced since at least 1989, in view of Sivam et al. (US Pat. No. 5,116,944). Moreover, those of skill in the art recognize, in view of Sivam et al., that albumin may be derivatized by reaction of a free NH2 group with the activated ester moiety of a heterobifunctional reagent such as SMCC and linked to a protein via reaction of a free sulfhydryl group on the protein with the maleimido or other appropriate reactive moiety of the heterobifunctional reagent. Alternatively, the protein may be derivatized with a heterobifunctional reagent and linked to albumin via reaction of a free sulfhydryl group on albumin with the maleimido or other appropriate reactive moiety of the heterobifunctional reagent. Hence, while the Examiner does not dispute Applicants contention that Peeter's methods would not produce the claimed conjugate, the Examiner recognizes that those of skill in the art recognize that methods of producing protein-albumin conjugates are limited to this specific example.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 63 be found allowable, claim 66 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight

difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

While Davidson et al. teaches a peptide and a method of using the patentably disclosed amino acid sequence represented by SEQ ID NO: 8 and 39, the reference does not teach or suggest administering the amino acid sequence with the addition of a succinimidyl-containing group or maleimido-containing groups. As such, claim 22, 25, 28, 33 and 61-62 appear to be free of the prior art and allowable.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Primary Examiner
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